

IN THE CLAIMS:

1. A method for delivering, by the subcutaneous route, a biologically active agent to a subject in need of said biologically active agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex,

 said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety,

 said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,

 said biologically active agent not forming a microsphere with said perturbant, and

 said perturbant being present in an amount effective for subcutaneous delivery of said biologically active agent; and

(c) subcutaneously administering said supramolecular complex to said subject.

2. A method as defined in claim 1, further comprising

(d) after said administering step, removing said perturbant from said supramolecular complex to transform said biologically active agent to said native state.

3. A method as defined in claim 2, wherein step (d) comprises diluting said supramolecular complex.

4. A method as defined in claim 1, wherein said intermediate state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.

5. A method as defined in claim 1, wherein said biologically active agent is selected from the group consisting of a peptide, a mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

Sub-a 6. A method as defined in claim 5, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

7. A method as defined in claim 1, wherein said perturbant comprises a proteinoid.

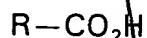
8. A method as defined in claim 1, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

9. A method as defined in claim 1, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

10. A method as defined in claim 1, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

11. A method as defined in claim 1, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

12. A method as defined in claim 1, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or a salt thereof.

13. A method for preparing a subcutaneously deliverable biologically active agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; and

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex,

said perturbant having a molecular weight ranging from about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety,

said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent;

said biologically active agent not forming a microsphere with said perturbant; and

said perturbant being present in an amount effective for subcutaneous delivery of said biologically active agent.

14. A method as defined in claim 13, wherein said intermediate state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.

15. A method as defined in claim 13, wherein said biologically active agent is selected from the group consisting of a peptide, a micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

Sub a2 16. A method as defined in claim 15, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II,

insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

17. A method as defined in claim 13, wherein said perturbant comprises a proteinoid.

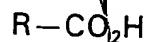
18. A method as defined in claim 13, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

19. A method as defined in claim 13, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

20. A method as defined in claim 13, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

21. A method as defined in claim 13, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

22. A method as defined in claim 13, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
a salt thereof

23. A subcutaneous delivery composition comprising a supramolecular complex comprising:

(a) a biologically active agent in an intermediate conformational state non-covalently complexed with

(b) a complexing perturbant having a molecular weight ranging from about 150 to about 600 and having at least one hydrophilic moiety and at least one hydrophobic moiety;

wherein said intermediate state is reversible to said native state and is conformationally between a native conformational and a denatured conformational state of said biologically active agent and said composition is not a microsphere; and said perturbant being present in an amount effective for subcutaneous delivery of said biologically active agent.

24. A composition as defined in claim 23, wherein said biologically active agent is selected from the group consisting of a peptide, a

micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

Claim 25

25. A composition as defined in claim 24, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

26. A composition as defined in claim 23, wherein said perturbant comprises a proteinoid.

27. A composition as defined in claim 23, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

28. A composition as defined in claim 46, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

29. A composition as defined in claim 23, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

30. A composition as defined in claim 23, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

31. A composition as defined in claim 23, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
a salt thereof.

32. A dosage unit form comprising:

- (A) a composition as defined in claim 23; and
- (B) (a) an excipient,
(b) a diluent,
(c) a disintegrant,
(d) a lubricant,
(e) a plasticizer,
(f) a colorant,
(g) a dosing vehicle, or
(h) any combination thereof.

33. A method for preparing an agent which is capable of being deliverable by the subcutaneous route to a subject in need of said agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex,

said perturbant having a molecular weight between about 150 and about 600 daltons, and having at least one hydrophilic moiety and one hydrophobic moiety,

said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,

said biologically active agent not forming a microsphere with said perturbant, and

said perturbant being present in an amount effective for subcutaneous delivery of said biologically active agent; and

(c) preparing a mimetic of said supramolecular complex.

34. A method as defined in claim 33, wherein said biologically active agent comprises a peptide and said mimetic comprises a peptide mimetic.

35. A method for preparing an agent which is capable of being delivered by the subcutaneous route to a subject in need of said agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate which

is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a perturbant to reversibly transform said biologically active agent to said intermediate state, wherein said perturbant being present in an amount effective for subcutaneous delivery of said biologically active agent; and

(c) preparing a mimetic of said intermediate state.

36. A method as defined in claim 35, wherein said perturbant comprises a pH changing agent, an ionic strength changing agent, or guanidine hydrochloride.

37. A subcutaneous delivery composition comprising a mimetic of the subcutaneous delivery composition prepared by the method of claim 13.

38. A method for delivering, by the sublingual route, a biologically active agent to a subject in need of said biologically active agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form a subcutaneously deliverable supramolecular complex,

said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety,

said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,

 said biologically active agent not forming a microsphere with said perturbant, and

 said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and

 (c) sublingually administering said supramolecular complex to said subject.

39. A method as defined in claim 38, further comprising

 (d) after said administering step, removing said perturbant from said supramolecular complex to transform said biologically active agent to said native state.

40. A method as defined in claim 39, wherein step (d) comprises diluting said supramolecular complex.

41. A method as defined in claim 38, wherein said intermediate state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.

42. A method as defined in claim 38, wherein said biologically active agent is selected from the group consisting of a peptide, a mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

July 4 43. A method as defined in claim 42, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a

monoclonal antibody, somatostatin, adrenocorticotropic, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

44. A method as defined in claim 38, wherein said perturbant comprises a proteinoid.

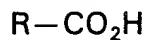
45. A method as defined in claim 38, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

46. A method as defined in claim 38, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

47. A method as defined in claim 38, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

48. A method as defined in claim 38, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

49. A method as defined in claim 38, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or a salt thereof.

50. A method for preparing a sublingually deliverable biologically active agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; and

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form a sublingually deliverable supramolecular complex,

said perturbant having a molecular weight ranging from about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety,

said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent;

said biologically active agent not forming a microsphere with said perturbant; and

 said perturbant being present in an amount effective for sublingual delivery of said biologically active agent.

51. A method as defined in claim 50, wherein said intermediate state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.

52. A method as defined in claim 50, wherein said biologically active agent is selected from the group consisting of a peptide, a micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

Sub A5 53. A method as defined in claim 52, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

54. A method as defined in claim 50, wherein said perturbant comprises a proteinoid.

55. A method as defined in claim 50, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

56. A method as defined in claim 50, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

57. A method as defined in claim 50, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

58. A method as defined in claim 50, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

59. A method as defined in claim 50, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to C_9 cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and naphthyl(C_2 to C_{10} alkenyl);

R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, $-CO_2R^1$, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1 to C_{10})alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or

a salt thereof.

60. A sublingual delivery composition comprising a supramolecular complex comprising:

(a) a biologically active agent in an intermediate conformational state non-covalently complexed with

(b) a complexing perturbant having a molecular weight ranging from about 150 to about 600 and having at least one hydrophilic moiety and at least one hydrophobic moiety;

wherein said intermediate state is reversible to said native state and is conformationally between a native conformational and a denatured conformational state of said biologically active agent and said composition is not a microsphere; and said perturbant being present in an amount effective for sublingual delivery of said biologically active agent.

61. A composition as defined in claim 60, wherein said biologically active agent is selected from the group consisting of a peptide, a micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

Subab 62. A composition as defined in claim 61, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

63. A composition as defined in claim 60, wherein said perturbant comprises a proteinoid.

64. A composition as defined in claim 60, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

65. A composition as defined in claim 60, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

66. A composition as defined in claim 60, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

67. A composition as defined in claim 60, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

68. A composition as defined in claim 60, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₈ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀)alkyl aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or a salt thereof.

69. A dosage unit form comprising:

- (A) a composition as defined in claim 60; and
- (B) (a) an excipient,
(b) a diluent,
(c) a disintegrant,
(d) a lubricant,
(e) a plasticizer,
(f) a colorant,
(g) a dosing vehicle, or
(h) any combination thereof.

70. A method for preparing an agent which is capable of being administered by the sublingual route to a subject in need of said agent, said method comprising:

- (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form a sublingually administrable supramolecular complex,
said perturbant having a molecular weight between about 150 and about 600 daltons, and having at least one hydrophilic moiety and one hydrophobic moiety,
said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,
said biologically active agent not forming a microsphere with said perturbant;
and
said perturbant being present in an amount effective for sublingual delivery of said biologically active agent; and

(c) preparing a mimetic of said supramolecular complex.

71. A method as defined in claim 70, wherein said biologically active agent comprises a peptide and said mimetic comprises a peptide mimetic.

72. A method for preparing an agent which is capable of being administered by the sublingual route to a subject in need of said agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a perturbant to reversibly transform said biologically active agent to said intermediate state, wherein said perturbant is in an amount effective for sublingual delivery of said biologically active agent; and

(c) preparing a mimetic of said intermediate state.

73. A method as defined in claim 72, wherein said perturbant comprises a pH changing agent, an ionic strength changing agent, or guanidine hydrochloride.

74. An oral delivery composition comprising a mimetic of the oral delivery composition prepared by the method of claim 50.

75. A method for delivering, by the intranasal route, a biologically active agent to a subject in need of said biologically active agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form an intranasally administrable supramolecular complex,

 said perturbant having a molecular weight between about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety,

 said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,

 said biologically active agent not forming a microsphere with said perturbant, and

 said perturbant being present in an amount effective for intranasal delivery of said biologically active agent; and

(c) intranasally administering said supramolecular complex to said subject.

76. A method as defined in claim 75, further comprising

(d) after said administering step, removing said perturbant from said supramolecular complex to transform said biologically active agent to said native state.

77. A method as defined in claim 76, wherein step (d) comprises diluting said supramolecular complex.

78. A method as defined in claim 75, wherein said intermediate state has a ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.

79. A method as defined in claim 75, wherein said biologically active agent is selected from the group consisting of a peptide, a mucopolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

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80. A method as defined in claim 79, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

81. A method as defined in claim 75, wherein said perturbant comprises a proteinoid.

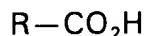
82. A method as defined in claim 75, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

83. A method as defined in claim 75, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

84. A method as defined in claim 75, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

85. A method as defined in claim 75, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

86. A method as defined in claim 75, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C_1 to C_{24} alkyl, C_2 to C_{24} alkenyl, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, phenyl, naphthyl, (C_1 to C_{10} alkyl)phenyl, (C_2 to C_{10} alkenyl)phenyl, (C_1 to C_{10} alkyl)naphthyl, (C_2 to C_{10} alkenyl)naphthyl, phenyl(C_1 to C_{10} alkyl), phenyl(C_2 to C_{10} alkenyl), naphthyl(C_1 to C_{10} alkyl) and naphthyl(C_2 to C_{10} alkenyl);

R being optionally substituted with C_1 to C_{10} alkyl, C_2 to C_{10} alkenyl, C_1 to C_4 alkoxy, -OH, -SH, $-CO_2R^1$, C_3 to C_{10} cycloalkyl, C_3 to C_{10} cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C_1 to C_{10} alkyl)aryl, aryl(C_1 to C_{10})alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R^1 is hydrogen, C_1 to C_4 alkyl or C_2 to C_4 alkenyl; or

a salt thereof.

87. A method for preparing an intranasally deliverable biologically active agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states; and

(b) exposing said biologically active agent to a complexing perturbant to reversibility transform said biologically active agent to said intermediate state and to form an intranasally administrable supramolecular complex,

said perturbant having a molecular weight ranging from about 150 to about 600 daltons, and having at least one hydrophilic moiety and at least one hydrophobic moiety,

said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent; and

said biologically active agent not forming a microsphere with said perturbant;

said perturbant being present in an amount effective for intranasal delivery of said biologically active agent.

88. A method as defined in claim 87, wherein said intermediate state has ΔG ranging from about -20 kcal/mole to about 20 kcal/moles relative to said native state.

89. A method as defined in claim 87, wherein said biologically active agent is selected from the group consisting of a peptide, a micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

*Sub
98*

90. A method as defined in claim 89, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

91. A method as defined in claim 87, wherein said perturbant comprises a proteinoid.

92. A method as defined in claim 87, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

93. A method as defined in claim 87, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

94. A method as defined in claim 87, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

95. A method as defined in claim 87, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

96. A method as defined in claim 87, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀ alkyl), or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
a salt thereof.

97. An intranasal delivery composition comprising a supramolecular complex comprising:

- (a) a biologically active agent in an intermediate conformational state non-covalently complexed with
- (b) a complexing perturbant having a molecular weight ranging from about 150 to about 600 and having at least one hydrophilic moiety and at least one hydrophobic moiety;

wherein said intermediate state is reversible to said native state and is conformationally between a native conformational and a denatured conformational state of said biologically active agent and said composition is not a microsphere; and said perturbant being present in an amount effective for intranasal delivery of said biologically active agent.

98. A composition as defined in claim 97, wherein said biologically active agent is selected from the group consisting of a peptide, a micropolysaccharide, a carbohydrate, a lipid, a pesticide, or any combination of the foregoing.

Sub 9 99. A composition as defined in claim 98, wherein said biologically-active agent is selected from the group consisting of human growth hormone, bovine growth hormone, growth hormone-releasing hormone, an interferon, interleukin-II, insulin, heparin, calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin, vasopressin, cromolyn sodium, vancomycin, desferrioxamine (DFO), or any combination of any of the foregoing.

100. A composition as defined in claim 97, wherein said perturbant comprises a proteinoid.

101. A composition as defined in claim 97, wherein said perturbant is selected from the group consisting of an acylated amino acid and an acylated poly amino acid.

102. A composition as defined in claim 97, wherein said perturbant is selected from the group consisting of a sulfonated amino acid and a sulfonated poly amino acid.

103. A composition as defined in claim 97, wherein said perturbant is selected from the group consisting of an acylated aldehyde of an amino acid and an acylated aldehyde of a poly amino acid.

104. A composition as defined in claim 97, wherein said perturbant is selected from the group consisting of an acylated ketone of an amino acid and an acylated ketone of a poly amino acid.

105. A composition as defined in claim 97, wherein said perturbant comprises a carboxylic acid having the formula



wherein R is C₁ to C₂₄ alkyl, C₂ to C₂₄ alkenyl, C₅ to C₁₀ cycloalkyl, C₅ to C₁₀ cycloalkenyl, phenyl, naphthyl, (C₁ to C₁₀ alkyl)phenyl, (C₂ to C₁₀ alkenyl)phenyl, (C₁ to C₁₀ alkyl)naphthyl, (C₂ to C₁₀ alkenyl)naphthyl, phenyl(C₁ to C₁₀ alkyl), phenyl(C₂ to C₁₀ alkenyl), naphthyl(C₁ to C₁₀ alkyl) and naphthyl(C₂ to C₁₀ alkenyl);

R being optionally substituted with C₁ to C₁₀ alkyl, C₂ to C₁₀ alkenyl, C₁ to C₄ alkoxy, -OH, -SH, -CO₂R¹, C₃ to C₁₀ cycloalkyl, C₃ to C₁₀ cycloalkenyl, heterocyclic having 3-10 ring atoms wherein the hetero atom is one or more atoms of N, O, S or any combination thereof, aryl, (C₁ to C₁₀ alkyl)aryl, aryl(C₁ to C₁₀)alkyl, or any combination thereof;

R being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and

R¹ is hydrogen, C₁ to C₄ alkyl or C₂ to C₄ alkenyl; or
a salt thereof.

106. A dosage unit form comprising:

- (A) a composition as defined in claim 97; and
- (B) (a) an excipient,
 - (b) a diluent,
 - (c) a disintegrant,
 - (d) a lubricant,

- (e) a plasticizer,
- (f) a colorant,
- (g) a dosing vehicle, or
- (h) any combination thereof.

107. A method for preparing an agent which is capable of being administered by the intranasal route to a subject in need of said agent, said method comprising:

(a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate conformational state which is reversible to said native state and is conformationally between said native and denatured states;

(b) exposing said biologically active agent to a complexing perturbant to reversibly transform said biologically active agent to said intermediate state and to form an intranasally administrable supramolecular complex,

 said perturbant having a molecular weight between about 150 and about 600 daltons, and having at least one hydrophilic moiety and one hydrophobic moiety,

 said supramolecular complex comprising said perturbant non-covalently complexed with said biologically active agent,

 said biologically active agent not forming a microsphere with said perturbant, and

 said perturbant being present in an amount effective for intranasal delivery of said biologically active agent; and

(c) preparing a mimetic of said supramolecular complex.

108. A method as defined in claim 107, wherein said biologically active agent comprises a peptide and said mimetic comprises a peptide mimetic.

109. A method for preparing an agent which is capable of being administered by the intranasal route to a subject in need of said agent, said method comprising:

- (a) providing a biologically active agent which can exist in a native conformational state, a denatured conformational state, and an intermediate which is reversible to said native state and is conformationally between said native and denatured states;
- (b) exposing said biologically active agent to a perturbant to reversibly transform said biologically active agent to said intermediate state, wherein said perturbant is in an amount effective for intranasal delivery of said biologically active agent; and
- (c) preparing a mimetic of said intermediate state.

110. A method as defined in claim 109, wherein said perturbant comprises a pH changing agent, an ionic strength changing agent, or guanidine hydrochloride.

111. An oral delivery composition comprising a mimetic of the oral delivery composition prepared by the method of claim 87.

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